

**Original Article**

**Ribavirin as a Beneficial Treatment Option for Hepatitis C Virus-associated Glomerular Disease**

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**ABSTRACT.** The management of hepatitis C virus (HCV)-induced glomerular disease remains unsatisfactory despite novel advances in antiviral and immunosuppressive therapy. Recent evidence highlighted the role of ribavirin, a drug provided with immunomodulatory properties, in the treatment of glomerular diseases associated with chronic HCV. We administered low-dose ribavirin (200 mg/day or 200 mg twice a week or 200 mg thrice weekly) in a prospective fashion to a group of patients with HCV-associated glomerular disease ( $n = 7$ ). Ribavirin monotherapy was given in most ( $n = 6$ ) patients and was accompanied by erythropoietin therapy in all. The primary endpoint was reduction of 24-h proteinuria after treatment ended; the secondary end-points were decrease in serum creatinine and amelioration of urinary abnormalities. We collected data on on-treatment adverse events (AEs), serious AEs, and laboratory abnormalities. Many patients ( $n = 6$ ) had inactive HCV infection as they had shown HCV RNA clearance from serum after antiviral therapy with direct-acting antivirals. Some patients ( $n = 4$ ) had membranoproliferative glomerulonephritis, the diagnosis being confirmed by kidney histology in three cases; others ( $n = 2$ ) received diagnosis of diabetic glomerulosclerosis, confirmed in one by kidney biopsy. We observed consistent reduction of 24-h proteinuria in two individuals after ribavirin therapy; another patient reported disappearance of microscopic hematuria. We found severe AE (hemolytic anemia) in three patients which required discontinuation of ribavirin treatment in two patients, one required hospitalization. Other AEs were cutaneous rash ( $n = 1$ ), dyspepsia ( $n = 1$ ), and fatigue ( $n = 1$ ). Low-dose ribavirin was able to give consistent reduction of 24-h proteinuria in two patients; tolerance to ribavirin was unsatisfactory. We need further studies aimed to expand our knowledge on ribavirin therapy of HCV-associated glomerular disease. The low incidence of the disease hampers the conduction of clinical trials on this aim.

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**Introduction**

Hepatitis C virus (HCV) infection is a common infectious disease, which has been recently estimated a prevalence of 71 million infected individuals all over the world.<sup>1</sup> In addition to

hepatic damage, HCV infection has been recently found to be involved in a variety of extrahepatic diseases; chronic HCV infection is associated with increased nonliver-related mortality compared to noninfected individuals.<sup>2</sup>

Kidneys are an important target of chronic HCV infection, and HCV can cause tubulointerstitial injury in a large case-control study;<sup>3</sup> however, the most frequent kidney disease associated with HCV remains HCV-associated glomerular disease. Despite recent achievements on the pathogenesis and natural history, the management of HCV-associated glomerular diseases remains a challenge to clinicians.<sup>4-6</sup> Interferon-based regimens have been given with some benefit.<sup>7,8</sup> The advent of all-oral, interferon (IFN)-free combinations of direct-acting antiviral agents (DAAs) gives us the possibility to make clearance of the virus with high efficacy, tolerability, and short treatment duration.<sup>9</sup> Unfortunately, the HCV RNA clearance is sometimes insufficient to improve the outcome of the disease,<sup>4</sup> and conventional (steroids, cyclophosphamide and azathioprine) or selective (rituximab) immunosuppression<sup>10</sup> is required to target the inflammation at glomerular level.

Some articles have underlined the efficacy of ribavirin monotherapy in the management of glomerular diseases associated with HCV<sup>11-14</sup> and hepatitis E virus<sup>15</sup> infections. We report in this article our experience (a prospective case series) on the efficacy and safety of ribavirin for HCV-associated glomerular disease.

## Material and Methods

### *Patients*

This was a study (prospective case series) of patients with HCV-associated glomerular disease recruited consecutively at our outpatient clinic between May 2010 and June 2018.

Inclusion criteria were the (1) evidence of chronic and active HCV infection and (2) presence of renal (glomerular) disease. Renal disease was defined either by the histologic finding of chronic glomerulonephritis (GN) at kidney biopsy or by the presence of at least two of the following clinical signs: proteinuria

and hematuria and reduced glomerular filtration rate ( $<60$  mL/min/1.73 m<sup>2</sup>) without alternative cause of chronic kidney disease (CKD). Cases with symptomatic mixed cryoglobulinemia syndrome are defined as showing HCV RNA levels  $>1000$  IU/mL at baseline and circulating cryoglobulins associated with clinical manifestations including purpura, cutaneous ulcers, Raynaud's phenomenon, arthralgias, sicca syndrome, gastrointestinal vasculitis, neurologic (peripheral neuropathy and/or central nervous system), or renal involvement. In this article, patients were included irrespective of their liver fibrosis stage, genotype, or prior HCV treatment status.

Exclusion criteria were as follows: conditions that might be associated with secondary cryoglobulinemia such as hematologic neoplastic disorders, autoimmune diseases, and acute or chronic infectious diseases not related to HCV; serious medical illnesses other than liver disease that might preclude completion of the study; hepatic failure, characterized by a history of bleeding esophageal varices, and a prothrombin time that was more than three times longer than normal; and cytopenia, as indicated by a platelet count below 3000/mm<sup>3</sup> or a hemoglobin level below 10 g/dL.

### *Laboratory assessments*

HCV infection was assessed in the form of a positive test for anti-HCV antibody; active (or viremic) HCV infection was defined by the presence of anti-HCV antibody and HCV viremia (detectable HCV RNA in serum) by the polymerase chain reaction (PCR). Circulating anti-HCV antibody was detected by third-generation enzyme-linked immunosorbent assay. HCV RNA levels were tested using Abbott real-time HCV PCR assay (Abbott, Wiesbaden, Germany) according to the manufacturer's protocol (detection limit of 12 IU/mL). Detection of HCV genotypes was performed using Versant HCV genotype assay kit (LiPA) 2.0 (Siemens Medical Solutions Diagnostics, Germany). This kit is a reverse hybridization line probe assay designed to identify HCV genotypes 1–6 in the 5' untranslated regions and core regions of HCV genome. The esti-

mated glomerular filtration rate (eGFR) was assessed by the Modification of Diet in Renal Disease 4-variable GFR equation. All measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT) were made by spectrophotometric method using the same automate. Proteinuria was measured by the ratio of urine protein to urine creatinine on a spot urine sample, when available. Otherwise, proteinuria was quantified by measuring the total quantity of protein in a 24-h urine collection test. Microscopic hematuria, dysmorphic red cells, and red cell casts were evaluated by examination of urine sediment by phase-contrast microscopy. Serum creatinine and urinary proteins were measured by standard methods. The serum concentrations of immunoglobulins, rheumatoid factor, and C<sub>3</sub> and C<sub>4</sub> complement components were measured by routine nephelometric assays. Normal ranges of biochemistries were as follows: albumin (3.4–4.8 g/dL), ALT (5–40 U/L), AST (5–38 U/L), C<sub>3</sub> (90–180 mg/dL), C<sub>4</sub> (10–40 mg/dL), creatinine (0.5–1.2 mg/dL), GGT (8–61 U/L), hemoglobin (13.5–17.5 g/dL), rheumatoid factor (1–14 IU/mL), total bilirubin (0.12–1.1 mg/dL), and total proteins (6.6–8.7 g/dL).

#### *Safety evaluation*

The patients were monitored on a regular basis for treatment efficacy and side effects. Patients underwent outpatient visits according to the following schedule: at the start of the study (baseline), and in the following weeks (week 2, 4, 6, 8, 12, 16, 20 and 24 after the start of therapy). The patients were seen at the end of therapy and on a regular basis (each month) post treatment. Each visit consisted of a query on medical history and side effects, check of concomitant medications, physical examination, laboratory analyses, and drug delivery. Laboratory analyses included blood chemistry, urine examination, and 24-h proteinuria.

The structure of recordings of adverse events (AEs) was as follows: any AEs or severe AE which included any event requiring hospitalization, life-threatening event, or death, and the

relationship with the administered medication was also assessed.

#### *Ethical standard*

All procedures during the study were conducted in accordance with the International Conference on Harmonization guidelines and ethical principles that have their origin in the Declaration of Helsinki. All patients enrolled in the study had given their informed consent in a written manner and received the drug on an off-label basis according to the local regulation. The study was reported according to the Enhancing the QUALity and Transparency Of health Research Network.<sup>16,17</sup>

## **Results**

#### *Baseline patient demographics*

The baseline demographic and clinical characteristics of patients included in the study group are shown in Table 1. The baseline clinical and biochemical characteristics of patients are reported in Table 2. All patients were male and Caucasian. Most patients had achieved clearance of HCV RNA from serum by DAAs – two patients had received antiviral therapy with sofosbuvir (SOF) + ribavirin and three SOF + ledipasvir + ribavirin.

In the subset of orthotopic liver transplant (OLT) recipients, the mean time between OLT and initiation of ribavirin therapy was  $58.7 \pm 51.8$  months. Treatment duration with ribavirin ranged between three and 53 months. The duration of follow-up after the end of ribavirin therapy was  $20.8 \pm 13.4$  months. Ribavirin therapy was accompanied by subcutaneous administration of erythropoietin-stimulating agents (ESAs) in all patients. At the beginning of ESA therapy, low dose was administered and subsequently increased according to hemoglobin levels.

Kidney biopsy was performed in four patients – we observed membranoproliferative GN ( $n = 3$ ) and diabetic glomerulopathy ( $n = 1$ ). Cryoglobulinemic disease with typical clinical and biochemical manifestations occurred in patient 2 and patient 5.

Three additional patients were recruited during

Table 1. Demographic and clinical patients' characteristics at baseline.

Characteristics	Patients (n = 7)
Age, years	62.7±6.8
Males, n	7 (100%)
Caucasian, n	7 (100%)
Patients listed for RT, n	1 (14%)
Liver transplant recipients, n	6 (86%)
Arterial hypertension, n	6 (86%)
Diabetes mellitus, n	2 (28%)
Decompensated cirrhosis, n	1 (14%)
AST (IU/L)	24.7±13
ALT (IU/L)	24.1±12.5
C <sub>3</sub>	105.2±24.4
C <sub>4</sub>	20.5±14.9
Rheumatoid factor (IU/L)	27.4±32.8
Serum creatinine (mg/dL)	1.95±0.73
24-h proteinuria	3.44±1.55
Detectable HCV RNA	1 (14%)
Urine sediment at phase-contrast microscopy	Microscopic hematuria (n=5), dysmorphic cells (n=2), and red cell casts (n=2)
HBsAg pos	1 (14%)
Anti-HIV pos	0
Hemoglobin, g/dL	11.7±1.62

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HCV: Hepatitis C virus, HBsAg pos: Hepatitis B surface antigen positive, HIV pos: Human immunodeficiency virus positive.

the study period but were not included as refused treatment with ribavirin. The latest update shows that all patients are alive with the exception of patient 6 (as reported below).

#### Efficacy outcomes

One patient (patient 1) did not show changes in proteinuria and serum creatinine during a 15-month ribavirin therapy (Figure 1). Percutaneous kidney biopsy had shown histological features of membranoproliferative (increased glomerular size, mesangial hypercellularity, and glomerular lobulated aspect) and chronic (tubular atrophy and glomerulosclerosis) GN.

Two patients obtained reduction of pro-

teinuria with ribavirin therapy. One patient (patient 2) lowered proteinuria, but this rebounded the following months after the end of ribavirin therapy (Figure 2). The proteinuria decrease was accompanied with amelioration of urine abnormalities (lower microscopic hematuria, dysmorphic cells, and red cell casts) and normalization of complement levels. He did not undergo kidney biopsy as he showed characteristic (biochemical and urinary) signs of membranoproliferative GN with clinical manifestations of cryoglobulinemic disease (purpuric rash and ulcers at the legs). Another patient (patient 3) had remission of proteinuria after combined antiviral therapy (pegylated IFN

Table 2. Adverse events experienced during treatment with direct-acting antiviral agents. Six of seven patients experienced at least adverse event.

Patients with HCV-associated GN	Number
Anemia requiring ESA only	2
Anemia requiring blood transfusions	1
Fatigue	1
Dyspepsia	1
Cutaneous rash	1

HCV: Hepatitis C virus, GN: Glomerulonephritis, ESA: Erythropoietin-stimulating agent

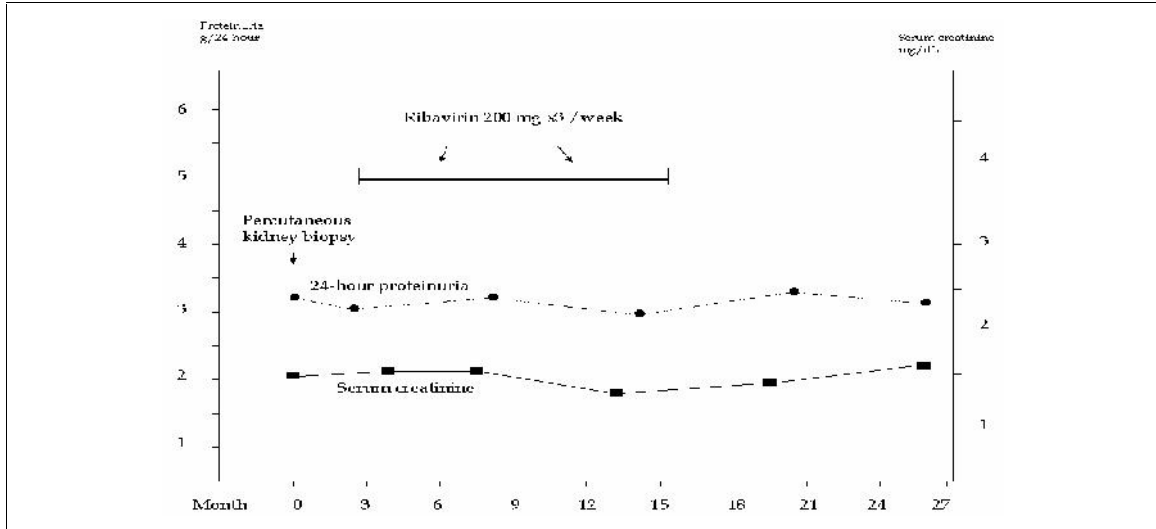


Figure 1. Efficacy outcome: Patient number 1. No impact of ribavirin on proteinuria or kidney function.

plus ribavirin) without viral response; he continued ribavirin monotherapy with some benefit (Figure 3). The patient had the histologic signs of membranoproliferative GN (large glomeruli with accentuation of lobules and irregular thickening of glomerular basement membrane by interposition of mesangial cells between endothelium and basement membrane) without crescents.

One patient (patient 4) prematurely abandoned ribavirin monotherapy due to important decrease in hemoglobin levels (he discontinued

therapy with ESA prematurely and on his own initiative). He was, therefore, hospitalized, received two units of concentrated red blood cells, and initiated maintenance hemodialysis (HD) in a few months (Figure 4). A few months after OLT (and immunosuppression with steroids, calcineurin inhibitors, and mycophenolate mofetil), he had developed a clinical picture of diabetic nephropathy that had been confirmed by kidney biopsy (diffuse and nodular marked expansion of the mesangium and increased glomerular basement

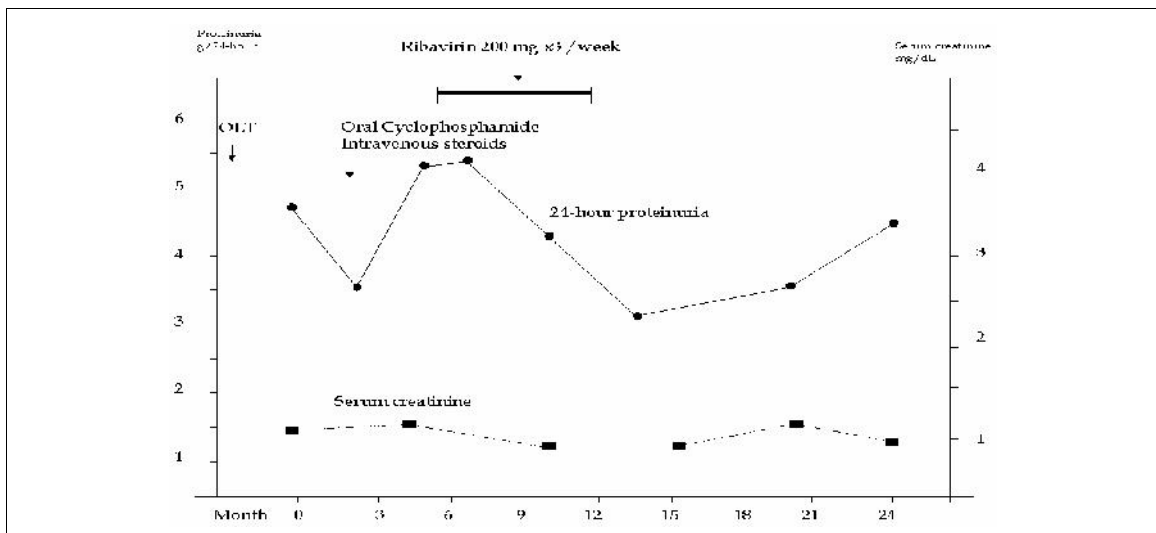


Figure 2. Efficacy outcome: Patient number 2. Lowered proteinuria after ribavirin monotherapy.

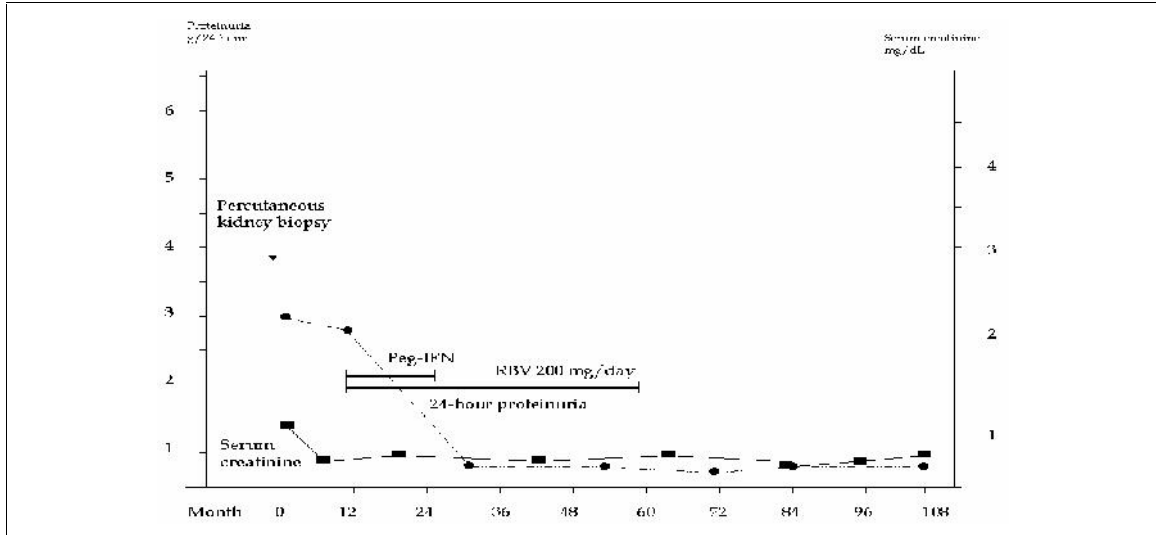


Figure 3. Efficacy outcome: Patient number 3. Proteinuria reduction after combined antiviral therapy (pegIFN plus RBV) before and RBV monotherapy after.

pegIFN: pegylated interferon, RBV: ribavirin.

membrane width). He is now doing well while on thrice-weekly maintenance HD.

Patient 5 had histologic and clinical (purpura) signs of cryoglobulinemic membranoproliferative GN; he achieved clinical benefit with high-dose intravenous steroids. Then, he received a course (11 months) of ribavirin therapy with poor benefit on serum creatinine and 24-h proteinuria (Figure 5). He is currently a liver transplant recipient and receives oral

corticosteroids, mycophenolate mofetil, and tacrolimus.

Patient 6 did not undergo kidney biopsy due to decompensated cirrhosis (HCV genotype 1b, HCV RNA titers 12,565,653 IU/mL). He showed typical signs of chronic nephritic syndrome – proteinuria (<1 g/day), stable kidney failure (serum creatinine 1.8 mg/dL), repeat urine sediment with microscopic hematuria (10–20 erythrocytes/microscopic field),

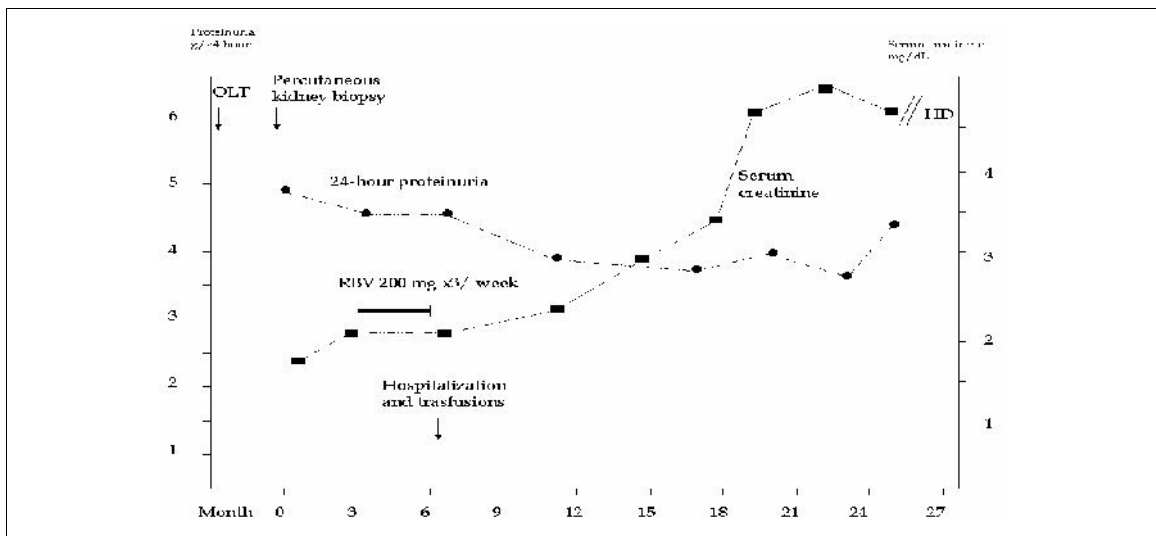


Figure 4. Efficacy outcome: Patient number 4. No impact of ribavirin on proteinuria or kidney function.

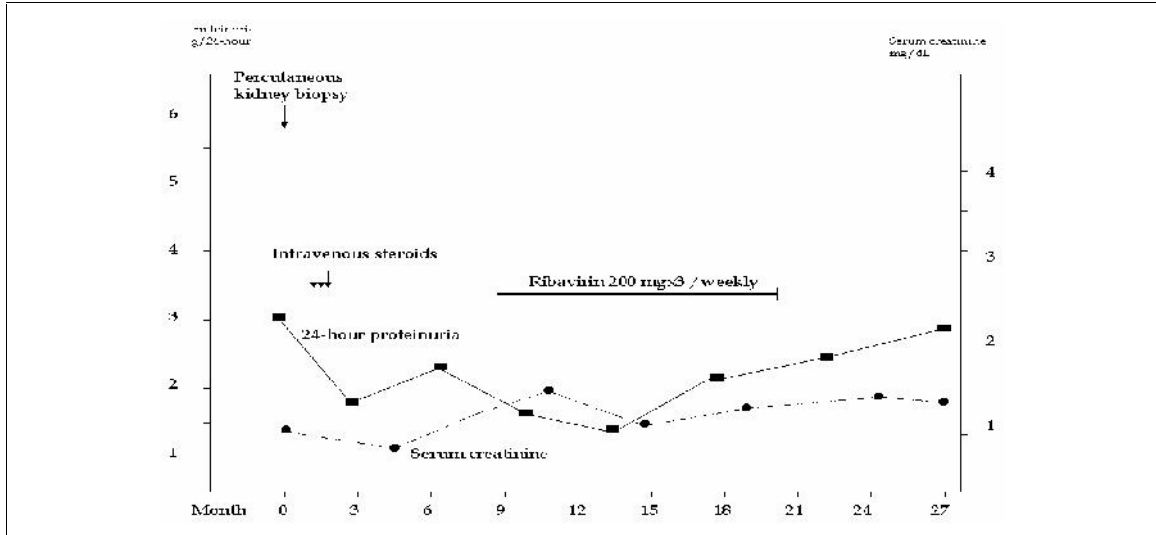


Figure 5. Efficacy outcome: Patient number 5.  
No impact of ribavirin on proteinuria or kidney function.

many dysmorphic erythrocytes, and casts (hyaline, granular, and red cell casts). He assumed ribavirin (very low doses, 200 mg twice weekly) due to his baseline hemoglobin values. No impact of ribavirin monotherapy occurred on serum creatinine and proteinuria, but a significant improvement of urine changes was found (disappearance of hematuria and red cell casts). Ribavirin monotherapy was interrupted due to low hemoglobin levels when he began the first cycle of evacuative paracentesis. He died due to complications related to the

onset of HCC (Figure 6).

Patient 7 showed an important increase of 24-h proteinuria (up to 12.7 g/day) immediately after OLT (serum creatinine increased to 2.5 mg/dL). He did not perform kidney biopsy due to the presence of an established clinical picture of diabetic nephropathy. He underwent monotherapy with low-dose ribavirin (200 mg thrice weekly) without apparent benefit on renal function or urine abnormalities; he suspended on its own initiative ribavirin (at week 13) while kidney function has shown progres-

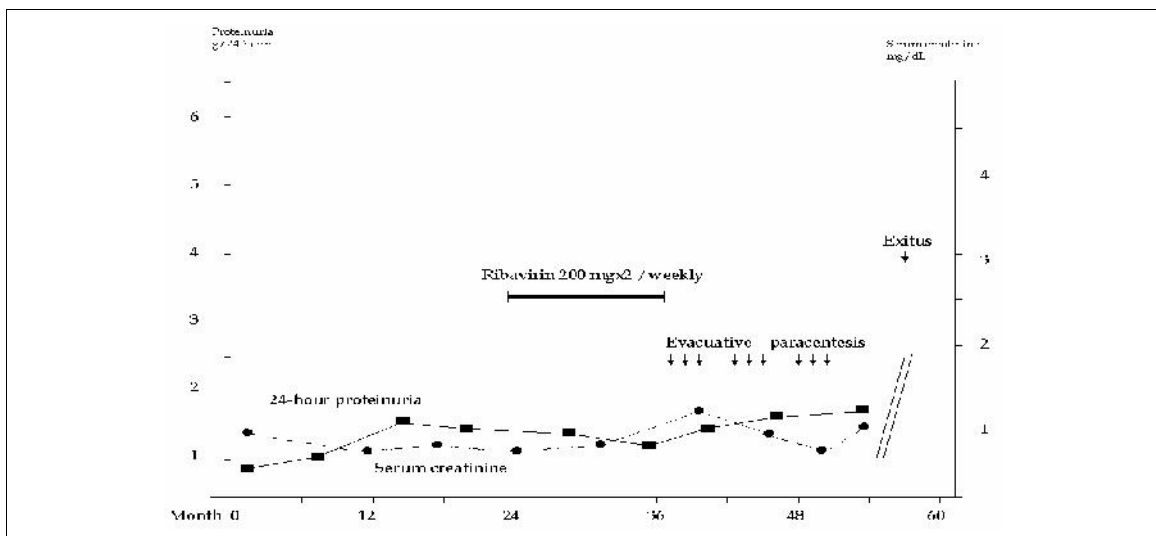


Figure 6. Efficacy outcome: Patient number 6.  
No impact of ribavirin on proteinuria or kidney function.

sive worsening (serum creatinine: 4.2 mg/dL). He was transferred to a nephrological unit near the home in order to initiate maintenance HD.

#### *Safety outcomes*

As listed in Table 2, AEs were recorded in almost all (6/7 = 86%) patients during treatment with ribavirin. Many AEs were mild, the most common being anemia ( $n = 3$ ) despite all patients used ESA during RBV therapy. One patient required hospitalization, ribavirin therapy was prematurely interrupted, and two units of packed red blood cells were administered – of note, he had not been compliant with erythropoietin therapy. Another dropout was again related to anemia (no hospitalization requested). One patient suffered from myocardial infarction, but this was not related to ribavirin therapy.

### **Discussion**

HCV infection can cause glomerular disease in both native kidneys and after kidney or liver transplant. The most common type of HCV-related glomerular disease is type I membranoproliferative GN usually, but not invariably, in the context of type II cryoglobulinemia. HCV-infected patients show less common glomerular diseases including membranoproliferative GN without cryoglobulinemia, membranous nephropathy, diabetic glomerulosclerosis, and others.<sup>14,18</sup>

Recent evidence had suggested the adoption of ribavirin therapy for patients with HCV-associated glomerular disease.<sup>11-14</sup> The results of our prospective case series confirm in part the results obtained in previous series – two patients experienced consistent reduction of proteinuria by ribavirin and three dropouts were observed.

Ribavirin was administered at low doses; monotherapy was adopted in most cases. We adopted low-dose ribavirin to avoid ribavirin accumulation and consequent hemolytic anemia as many patients in the current case series had impaired kidney function at baseline. Hemolytic anemia can be particularly dangerous in CKD patients as they often have

anemia as well as other comorbidities (for example, cardiac ischemia) at baseline.

Two patients interrupted the treatment with ribavirin due to an important reduction of hemoglobin levels; one of them required hospitalization and recovered after transfusions with red blood cells. Of note, this patient discontinued erythropoietin therapy which had been prescribed at the time of ribavirin initiation. Thus, the side effect profile of our case series gives emphasis to the recommendations made by the KDIGO HCV Work Group. It had been suggested low-dose ribavirin, frequent monitoring of hemoglobin levels, and therapy with ESA to prevent anemia induced RBV.<sup>19</sup>

We suggest that the antiproteinuric activity of ribavirin was related to its immunomodulatory activities. Ribavirin is a guanosine (ribonucleic) analog that produces broad-spectrum activity against several RNA or DNA viruses. Although originally approved for the treatment of severe respiratory syncytial virus, RBV has been used in the treatment of various viruses including HCV.<sup>20</sup> Ribavirin's antiviral activity has been postulated to result from four pathways; the last is given by immunomodulation of shifting a Th2 response in favor of a Th1 phenotype. In humans, ribavirin has been seen to enhance HCV-specific Th1 response by increasing IFN-gamma and tumor necrosis factor-alpha (TNF- $\alpha$ ) production by peripheral blood mononuclear cell (PBMC) in patients with chronic HCV. In addition, ribavirin increased Th1 cytokine production [IFN-gamma, interleukin 2 (IL-2), and IL-12] and TNF-alpha production in PBMC of patients with chronic HCV.<sup>20</sup>

We need randomized clinical trials (RCTs) in order to clarify the efficacy and safety of ribavirin in the treatment of HCV-associated glomerular disease; the low incidence of the disease prevents the conduction of clinical studies on this point. We need to clarify several points – as an example, it remains unclear if the impact of ribavirin on proteinuria is dose dependent or not. The duration of ribavirin monotherapy and the predictors of response to ribavirin are still unknown.

In conclusion, our prospective case series



confirms partially those obtained previously by other authors on the management of HCV-associated glomerular disease. The safety profile was unsatisfactory in our study; a careful monitoring of hemoglobin values and renal function is suggested. We need further studies, both RCTs and “real-life” cohorts, to evaluate the efficacy and safety of immunomodulatory agents such as RBV in the treatment of glomerular disease-associated with HCV.

**Conflict of interest:** Dr. Fabrizio Fabrizi is a consultant or advisor to AbbVie, Merck & Co.

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